REMARKS

Claims 1-9, 21-25, 34, 36, 38, 39, 42-44, and 47-91 are pending in the present application. By the present Amendment, claims 1-8, 34, 38, 39, 42-44, 47-51, 55, 58, 59, 62-65, 68, 70-71, 74-76, and 79-91 have been canceled, without prejudice to refile.

1. **Para. 3 of the Office Action – Objection to Embedded Hyperlink**

The Examiner objected to the specification because it contains an embedded hyperlink and/or other form of browser executable code on page 31, lines 12 and 33, page 32, line 5 and page 46, lines 1 and 3. The Examiner suggested that the hyperlinks be deleted from the specification.

The specification has been amended to remove the hyperlinks. Care has been taken so that no new matter has been added. The Applicants respectfully assert that this objection has been successfully overcome.

2. **Para. 4 of the Office Action – Objection to Claim 68**

The Examiner objected Claim 68 for being drawn in part to canceled claims 40 and 41. Unrelated to patentability, Applicants have canceled claim 68, without prejudice to refile, solely to obtain expeditious allowance of the instant application, thereby rendering this objection moot.

3. **Para. 5 of the Office Action – Objection to claim 75**

The Examiner objected Claim 75 for reciting "which comprises which comprises." Unrelated to patentability, Applicants have canceled claim 75, without prejudice to refile, solely to obtain expeditious allowance of the instant application, thereby rendering this objection moot.

4. **Para. 6 of the Office Action – Rejected Under 35 U.S.C. Section 112, Second Paragraph**

The Examiner rejected claims 8, 21-25, 36, 44, 51-57, 60, 61, 66, 67, 73-78, 84, 85, and 90 under 35 U.S.C. Section 112, second paragraph, for allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicants regard as their invention. The Examiner alleges that claims 8, 44 and 83 and dependant claims 51-54, 56, 57, 60, 73-76, 84, 98, and 90 are rendered vague and indefinite by reference to a trade name.

Unrelated to patentability, Applicants have canceled claims 8, 44 and 83, without prejudice to refile, solely to obtain expeditious allowance of the instant application, thereby rendering this objection moot.

The Examiner rejected claims 21, 22, 23, 24, and claims 25, 36, 66, 77 and 78 dependant therefrom because allegedly the metes and bounds of the "amounts" cannot be set. The Examiner is invited to review MPEP 2173.05(c)(III) "EFFECTIVE AMOUNT." As discussed in this section of the MPEP, the proper test to determine if the phrase "effective amount" is definite is "whether or not one skilled in the art could determine specific values for the amount based on the disclosure." MPEP 2173.05(c)(III). The MPEP further goes on to state that "the more recent cases have tended to accept a limitation such as "an effective amount" as being definite...." As the Examiner herself indicates in the Office Action dated February 20, 2004, paragraph 6, some considerations in determining the "amounts" to one of skill in the art may be "a function of the size of the host, the route of administration and amount of pathological tissue present within the host." The specification of the present application provides ample guidance to determine the "amounts" at least on pages 41, line 12 ("5.9.1 EFFECTIVE DOSE") thru page 44, line 24 ("5.9.2 FORMULATIONS"). Further, at least Example 7.1.2 on page 50, line 25 thru page 51, line 21 and Figures 8A-C discuss and show the results from the intra-peritoneal injection of 1 mg/kg of S2C6 IgG. At least this Example and Figures coupled with the "EFFECTIVE DOSE" section of the application would provide ample disclosure to one of skill in the art to determine the specific values.

The Examiner rejected claims 55 and 56 for allegedly being unclear whether "the "binding domain of the antibody" is referring to the domain which binds the Fc receptor, such as the human immunoglobulin constant domain, or if the domain is referring to the antigen binding domain." Claim 55 has been canceled rendering the rejection to this claim moot. Claim 56 has been amended to depend from claim 9. Claim 9 recites "a human immunoglobulin constant domain." Since claim 56 depends from claim 9, claim 56 further defines the invention in claim 9. By the process of claim differentiation, claim 56 refers to a domain which is different than "a human immunoglobulin constant domain" (*e.g.* the epitope binding domain).

5. Para. 7 of the Office Action – Rejected under 35 U.S.C. Section 112, First Paragraph

The Examiner rejected claims 6, 9, 22, 24, and 86 under 35 U.S.C. Section 112, first paragraph as allegedly failing to comply with the enablement requirement. The Examiner further rejected claims 25, 38, 47-50, 52-54, 56-58, 66, 73, 78, 87, 88, and 91 in part as they depend on claims 6, 9, 22, 24, and 86. The Examiner alleges that the claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains to make and/or use the invention. Particularly, the Examiner alleges that the Applicants referral to the deposit of the hybridoma secreting the S2C6 antibody on page 58 of the specification is insufficient assurance that all the conditions of 37 CFR 1.801-1.809 have been met.

The Applicants have previously provide in the present application a "Statement of Attorneys for Applicants Regarding Permanence and Availability of Deposited Microorganisms" dated April 18, 2001 with the filing of the Amendment under 37 C.F. R. § 1.111 dated February 28, 2002. A duplicate copy of this Statement stating that the deposit has been accepted by an International Depository authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposits will be irrevocably removed upon the grant of a patent on this application, and that the deposit will be replaced if viable samples cannot be dispensed from the depository, is provided with the present Amendment. Applicants respectfully assert that this rejection of the Examiner has successfully been overcome.

6. Para. 8 of the Office Action – Rejection of claims 21, 22, 25, 36, 66, 77, and 78 under 35 U.S.C. Section 112, First Paragraph

The Examiner rejected claims 21, 22, 25, 36, 66, 77, and 78 under 35 U.S.C. Section 112, first paragraph, for allegedly failing to reasonably provide enablement methods for preventing cancer while the Examiner admits that the specification is enabling for methods of treating cancer.

Applicants do not concede to the Patent Office position; Applicants are amending the claims solely to obtain expeditious allowance of the instant application. Applicants have amended claims 21, 22, and 36 to remove preventing. By this amendment,

Applicants expressly do not disclaim equivalents of the invention. The Applicants respectfully assert that the Examiner's rejection has been successfully overcome.

7. **Para. 9 of the Office Action – Rejection of claims 36 and 61 under 35 U.S.C. Section 112, First Paragraph**

The Examiner rejected claims 36 and 61 under 35 U.S.C. Section 112, first paragraph, for allegedly failing to reasonably provide enablement for a method of treating an immune disorder while the Examiner admits that the specification is enabling for methods of treating cancer, and/or activating or augmenting an immune response against a cancer antigen or cancer cell.

Applicants do not concede to the Patent Office position; Applicants are amending the claims solely to obtain expeditious allowance of the instant application. Applicants have amended "or an immune disorder" from claim 36. By this amendment, Applicants expressly do not disclaim equivalents of the invention. The Applicants respectfully assert that the Examiner's rejection has been successfully overcome.

8. **Para. 10 of the Office Action –Rejection of claims 8, 36, 51-53, 56, 57, 69-73, 44, 74-76, 79, 83-85 and 90 under 35 U.S.C. Section 112, First Paragraph**

The Examiner rejected claims 8, 36, 51-53, 56, 57, 69-73, 44, 74-76, 79, 83-85 and 90 under 35 U.S.C. Section 112, first paragraph, for allegedly failing to comply with the written description requirement. The Examiner recites that allegedly the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. More particularly, in paragraph 10(A), the Examiner alleges that the claims encompass molecules which are not proteins or antibodies, and which bind to an epitope of CD40 which is not the epitope to which the S2C6 antibody binds. Applicants respectfully traverse this rejection.

Applicants do not concede to the Patent Office position; Applicants are amending the claims solely to obtain expeditious allowance of the instant application. Applicants have canceled claims 8, 44, 51, 70-71, 74-76, 79, 83-85 and 90, without prejudice to refile, thereby rending the rejection to these claims moot.

As discussed in the Revised Interim Written Description Guidelines Training Materials, available from the United States Patent and Trademark Office web page at

http://www.uspto.gov/web/menu/written.pdf, "[t]here is a strong presumption that an adequate written description of the claimed invention is present in the specification as filed." (see page 4, lines 7-8 of the Written Description Guidelines). Example 16 is directed to antibodies. (see pages 59-60 of the Written Description Guidelines). As in Example 16, the present specification teaches that CD40 (antigen X) has been isolated and is expressed on a variety of cell types, including B cell malignancies. (see at least pages 1-2 of the specification). As in Example 16, the present specification discusses the use of a CD40-Ig and soluble CD40 on at least pages 52-54 of the present specification. The present specification *goes beyond* the specification described in Example 16 and actually discloses example antibodies which bind to CD40 (i.e. S2C6) and asserts that these antibodies can be used in the treatment of cancer and immune disorders. Example 16 goes on to state that:

> The general knowledge in the art is that such antibodies are structurally well characterized. It is well known that all animals produce antibodies and they exist in five isotypes, IgM, IgG, IgD, IgA, and IgE. Antibodies contain an effector portion which is the constant region and a variable region which contains the antigen binding sites in the form of complementary determining regions and framework regions. The sequence of constant regions as well as the variable regions subgroups (framework regions) from a variety of species are known and published in the art. It is also well known that antibodies can be made against virtually any protein....The level of skill and knowledge in the art of antibodies at the time of filing was such that production of antibodies against a well-characterized antigen was conventional. This is mature technology where the level of skill is high and advanced.

As in Example 16, one of skill in the art would have recognized the spectrum of antibodies which bind to CD40 were disclosed as a result of isolation of CD40. Therefore, as in Example 16 of the Written Description materials, claims 36 and 69, and any claims dependant therefrom, as amended to recite "an antibody," meets the requirement under 35 U.S.C. 112, first paragraph, as providing adequate written description of the claimed invention. Applicants respectfully assert that this amendment successfully overcomes the Examiner's rejection.

In paragraph 10(B), the Examiner rejects claims 8, 44, 73, 74, 76, 83, 84, 85, and 90 for allegedly lacking written description. Applicants have canceled claims 8, 44, 74, 76, 83-85 and 90, without prejudice to refile, thereby rending the rejection to these claims

moot. Claim 73 has been amended to depend from claim 9, thereby rendering the rejection to this claim moot. Applicant respectfully asserts that this rejection has successfully been overcome.

9. **Paragraph 11 of the Office Action -- Rejection of Claims 1-3, 6-9, 21-24, 38, 39, 42-44, 47-66, 68-71, 74-76, 82 and 86-88 under 35 U.S.C. 103(a) as allegedly being unpatentable over Melief et al (US Application 2003/0022860) in view of de Boer (U.S. Patent No. 5,874,082).**

The Examiner rejected claims 1-3, 6-9, 21-24, 38, 39, 42-44, 47-66, 68-71, 74-76, 82 and 86-88 under 35 U.S.C. 103(a) as allegedly being unpatentable over Melief et al (US Application 2003/0022860) in view of de Boer (U.S. Patent No. 5,874,082). The Applicant respectfully traverses the rejection.

Applicants do not concede to the Patent Office position; Applicants are amending the claims solely to obtain expeditious allowance of the instant application. Applicants have canceled claims 1-3, 6-8, 38, 39, 42-44, 47-51, 55, 58, 59, 62-65, 68, 70-71, 74-76, 82 and 86-88, without prejudice to refile, thereby rending the rejection to these claims moot.

The Examiner alleges that Melief et al teach

> "a method of treating cancer comprising the administration of CD40 binding molecules (abstract, claims 5-9, 11-13). Melief et al teach that the "triggering" of CD40 in vivo can replace the requirement of a T-cell helper signal (examples 1 and 2 [0045]) and concludes that CD40 activation in the presence of tumor derived peptide reverses peripheral tolerance and results in tumor specific immunity (lines 22-24 of [0045]). Melief et al teach that the CD40 binding molecules include antibodies [0008] and that humanized antibodies are preferred for the treatment of human subjects [0030]. Melief et al teach that the administration of CD40 binding molecules enhances the efficacy of anti-cancer vaccines comprising tumor specific peptides [0047]. Melief et al teach FGk45 as a CD40 activating antibody (line 5 of [0020]."

The Examiner admits that Melief et al do not teach the administration of a humanized S2C6 antibody for the treatment of cancer.

The Examiner alleges that de Boer teaches:

> "that anti-CD40 antibodies known in the art [prior to the disclosure of de Boer] have a stimulatory effect on human B cells (column 2, lines 45-46 and 62-64). de Boer teaches that the prior art anti-CD40 antibodies mimic the effect of T-helper cells and thus can replace the T cell helper signal (column 2, lines 51-59). de

> Boer teaches 'new' antibodies such as 5D12, 3C6, and 3A8 which differ from the prior art anti-CD40 antibodies in that the new antibodies inhibit the B-cell stimulatory response (column 2, lines 62-67). de Boer teaches S2C6 as an "old" antibody (in contrast to the "new" antibodies) which stimulates B-cell proliferation (column 17, lines 57-62, and the description for Figures 5 and 6). de Boer teaches that the "new" antibodies can inhibit stimulatory signals elicited by the "triggering" of CD40 with another antibody (column 18, lines 36-40). One of skill in the art would reasonably conclude that the "old" S2C6 antibody "triggers" CD40. de Boer teaches that the administration of humanized versions of the "new" antibodies would be efficacious in the treatment of antibody-mediated autoimmune diseases (column 3, lines 52-65 and column 4, lines 14-19)."

The Examiner admits that S2C6 and the antibodies disclosed by de Boer are different in structure and function (page 8 of the Office Action, lines 12-14).

A. No Motivation to Combine References

Applicants submit that the subject matter of these claims is not obvious over this combination of references because the Examiner has provided no motivation for making this combination, as required by MPEP 2142-2144.. These sections of the MPEP specifically establish the requirement that there must be a suggestion or motivation to modify the cited references to support a rejection for obviousness. As stated in the MPEP:

> "[o]bviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art." (MPEP 2143.01, quoting from In re Fine, 837 F.2d 1071, 5 U.S.P.Q. 2d 1596 (Fed. Cir. 1988).

Further, MPEP 2143.01 citing In re Mills, 916 F.2d 680, 16 U.S.P.Q.2d 1430 (Fed. Cir. 1990 :

"[t]he mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination." (emphasis in the original).

These MPEP sections are in accord with numerous well-established precedents. *In re Geiger*, 815 F. 2d 686, 2 U.S. P. Q. 2d 1271 (Fed. Cir. 1987); *N.V. Akzo v. E.I. du Pont de Nemours*, 810 F.2d 1148, 1 U.S. P.Q. 2d 1704 (Fed. Cir 1987); *In re Farrell*, 853 F.2d 894, 7 U.S.P.Q. 2d 1673 (Fed. Cir. 1988). The Examiner is using

impermissible hindsight and is making a piecemeal rejection. The Applicants respectfully assert that the Examiner cannot, with the present application and claims as a guide, piece together a variety of publications which by themselves or in combination have no motivation to combine, to render the present claims obvious. It is wrong to use the claims under consideration as a guide through the maze of publications and patents, combining the right publications and patents in the right way so as to achieve the result of the claims in the current application. *Orthopedic Equipment Co. v. United States, 702 F.2d 1005, 217 U.S.P.Q. 193 (Fed.Cir. 1983).*

B. Improper to Combine References Which Teach Away from the Claims; de Boer does not satisfy the deficiencies of Melief and the combination of Melief and de Boer cannot render claims 1-3, 6-9, 21-24, 38, 39, 42-44, 47-66, 68-71, 74-76, 82 and 86-88 obvious under 35 U.S.C. 103(a).

It is improper with an obviousness rejection to combine two references if one of the references teaches away from the claimed invention. Where a reference warns against rather than teaches the invention, one cannot be expected to combine it with another teaching. (In re Fine, 837 F.2d 1071, 5 USPQ 1596 (Fed. Cir. 1988). As stated in paragraph 2141.02 of the MPEP, "a prior art reference must be considered in its entirety, i.e., as a whole, including portions which would lead away from the claimed invention." MPEP paragraph 2141.02 provides the following example of a teaching away:

> Claims were directed to a process of producing a porous article by expanding shaped, unsintered, highly crystalline poly(tetrafluoroethylene) (PTFE) by stretching said PTFE at a 10% per second rate to more than five times the original length. The prior art teachings with regard to unsintered PTFE indicated the material does not respond to conventional plastics processing, and the material should be stretched slowly. A reference teaching rapid stretching of conventional plastic polypropylene with reduced crystallinity combined with a reference teaching stretching unsintered PTFE would not suggest rapid stretching of highly crystalline PTFE, in light of the disclosures in the art that teach away from the invention, i.e., that the conventional polypropylene should have reduced crystallinity before stretching, and that PTFE should be stretched slowly.

A reference may be said to teach away when a person of ordinary skill, upon reading it, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path taken by the inventor (Monarch

Knitting Mach. Corp. v. Sulzer Morat Gmbh, 139 F.3d 877, 45 USPQ 1977 (Fed. Cir. 1998); Para-Ordnance Mfg. v. SGS Importers Int'l, Inc., 73 F.3d 1085, 37 USPQ 1237 (Fed. Cir. 1995); In re Gurley, 27 F.3d 551, 31 USPQ 1130 (Fed. Cir. 1994).) Melief et al teach away from the claimed invention because Melief et al *specifically and particularly teach away from* a *CD40 on B-cells* (see paragraph [0040] of Melief).

Melief et al discusses the "licensing model" of CTL activation (*See* para. [0004], lines 1-11 of Melief et al.). Briefly, in the licensing model, T-helper cells recognize a specific antigen on professional antigen-presenting cells (APCs), and deliver a signal that activates, or 'licenses', the APC (*See* para. [0004], lines 5-11 of Melief et al). This activated APC can then stimulate T-killer cells to mount a response against that antigen. More particularly, Cytotoxic T lymphocytes (CTLs) which carry the CD8 antigen recognize antigens that are presented on target cells by the class I major histocompatibility complex. CTLs are responsible for the killing of antigen-bearing target cells, such as virus-infected cells or cancer cells (see para. [0003], lines 1-3 of Melief et al.). Although CTL effectors can act alone when killing target cells, their differentiation from naive CD8-positive T cells is often dependent on 'help' from CD4-positive helper T (T_H) cells. Melief et al describe that "... the T-helper cell is not providing helper signals directly to the CTL...but rather, the T-helper cell is providing a signal to the DC that induces yet uncharacterized cell surface and/or soluble molecules that can activate CTL in the absence of T-helper cells." (see para. [0002], lines 9-14). To generate an immune response, antigen-specific T-helper and T-killer cells must find each other. They are brought together by an antigen-loaded cell, such as a dendritic cell (see para [0002] lines 14-16 and para. [0007], lines 6-8 of Melief et), that displays antigens to both. As stated in Melief "[t]he signal provided by the T-helper cell to the DC is mediated by CD40-CD40L." Para. [0002], lines 15-17. In the licensing model, the T helper cell can first engage and 'condition' the dendritic cell which then becomes empowered to stimulate a killer cell. As stated in Melief et al "interaction between T-helper cell and DC through the CD40-CD40L binding results in activation of the DC, thereby enabling the DC to efficiently prime naïve CTL" (para. [0004], lines 15-18 of Melief et al.) wherein the T-helper cells express CD40L (see para. [0010, lines 7-9 of Melief et al) and the DC cells express CD40 (see para. [0007], lines 6-8 of Melief et al). Melief et all discusses "...*the*

CD40 pathway on DC is responsible for the induction of anti-tumor CTL responses." (para. [0007, lines 6-8 of Melief et al.) (emphasis added).

This "licensing model" is further elucidated in Figures 3a, 3b, and 3c. Paragraph [0017] of Melief et al. The legend for Figure 3 is "*B cells are not essential* as cross-priming APCs or for anti-CD40 mediated restoration of cross-priming." (emphasis added).

The experiment represented in Figures 3a, 3b, 3c was conducted to investigate whether B cells had a role in the restoration of CTL priming by treatment with CD40 activating antibodies. As shown in Figure 3c, which depicts cell lysis approaching about 75% to 90% in CD4 depleted/B cell deficient/treated with the CD-40 activating antibody FGK45 mice, *B cells are not necessary* in the restoration of CTL priming by treatment with CD40 activating antibodies. Melief et al does not teach CD40 being found on B cells. Rather, in this licensing model, CD40 is found on dendritic cells.

Figures 3a, 3b, and 3c are further described in Melief et al in Example 1 "Signaling through CD40 can replace $CD4^+$ helper T cells in CTL, priming." (*See*, para. [0037]-[0040] of Melief et al.) Melief et al actually *teach away from* a molecule as claimed which "increases the binding of CD40 ligand to cell surface CD40 *on B cells*" as claimed in claims 9, 21-24, 36 and 39. Melief et al, in paragraph [0040] state as follows "...B cells *are not required* as APC or accessory cells for cross-priming in this model system, *nor are they required* for CD40-mediated restoration of cross priming of CTLs in the absence of CD4+ helper T cells." (emphasis added). To address the suggestion that B cells have a role in the restoration of CTL priming by treatment with CD40 activating antibodies (the only example in Melief et al of an activating antibody being FGK45 monoclonal antibody), B6 MT mice (mice which lack mature B cells) were immunized with allogeneic Ad5EI-BALB/ MECs. Melief et al allege that mature B cells were not needed for cross priming of EIB-specific CTLs. Even in the absence of CD4+ cells in mice with depleted B cells, B cells were not needed for the priming of EIB-specific CTLs in the presence of FGK45 monoclonal antibody. Thus, Melief et al teach away from a molecule which increases the binding of CD40 ligand to cell surface CD40 on B cells by at least 45 % since B cells are not needed in Melief's model system.

This is directly opposite of what is taught in de Boer, *i.e.* that CD40 is found on B-cells. Since the Melief et al and de Boer teach opposite things, the two references

cannot be properly combined. de Boer does not satisfy the deficiencies of Melief et al and one would not look to the disclosure of de Boer to satisfy the deficiencies of Melief et al. First, Melief et al teach away from CD40 being found on the surface of B-cells. In direct opposition, de Boer teaches that CD40 is found on the surface of B-cells. Second, de Boer places S2C6 in the group of antibodies which stimulates human B-cells. However, Melief does not even disclose CD40 on B-cells, let alone the stimulation of B-cells. The functions of the antibodies of de Boer compared to the function of the "old" antibodies, as admitted by the Examiner on page 9 of the current Office Action, are in opposition. The de Boer antibodies inhibit stimulation of B-cells whereas the "old" antibodies, into which the Examiner groups S2C6, stimulate B cells. However, B-cells are not even required in the process of antigen presentation as described in Melief et al. One who is seeking to increase the proliferation of B-cells, as antibody S2C6 does, would not look to two disclosures which disclose (a) no need for B-cells (Melief et al) and (b) the inhibition of the proliferation of B-cells (de Boer). Third, de Boer teaches that the antibodies of his invention **block** CD40L/CD40 interaction (col. 12, lines 66-67 through col. 13, lines 1-2 of de Boer) rather than "increases the binding of CD40 ligand to cell surface CD40 *on B cells*" as claimed. Therefore, Applicants respectfully assert that claims 9, 21-24, 52-54, 56, 57, 60, 61, 66, and 69 are unobvious under 35 U.S.C. 103(a) over Melief et al in view of de Boer. Applicants respectfully request withdraw of the rejection.

9. **Paragraph 12 of the Office Action – Rejection of Claims 1-3, 6-9, 21-24, 34, 38, 39, 42-44, 47-66, 68-71, 74-76, 82 and 86-88 under 35 U.S.C. Section 103(a) as being unpatenable over Melief (U.S. application No. 2003/0022860) and de Boer (U.S. 5,874,082) in view of Clark (Protein Engineering of Antibody Molecules for Prophylactic and Therapeutic Applications in Man).**

The Examiner rejected claims 1-3, 6-9, 21-24, 34, 38, 39, 42-44, 47-66, 68-71, 74-76, 82 and 86-88 under 35 U.S.C. Section 103(a) as being unpatenable over Melief et al (U.S. application No. 2003/0022860) and de Boer (U.S. 5,874,082) in view of Clark. The Examiner recites that it would have been "prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to make the antibody rendered obvious

by the teachings of Melief et al and deBoar [sic] et al having any constant region." The Applicants respectfully traverse this rejection.

Applicants do not concede to the Patent Office position. Applicants are amending the claims solely to obtain expeditious allowance of the instant application. Applicants have canceled claims 1-3, 6-8, 34, 38, 39, 42-44, 47-51, 55, 58. 59, 62-65, 68, 70-71, 74-76, 82 and 86-88, without prejudice to refile, thereby rending the rejection to these claims moot.

Clark merely suggests IgG isotypes. Claim 34 has been canceled. As discussed above, claims 9, 21-24, 52-54, 56, 57, 60, 61, 66, and 69 are non-obvious over Melief et al in view of de Boer, and Clark does not satisfy the deficiencies of Melief et al and de Boer. Applicants respectfully request withdraw of the rejection.

10. Paragraph 13 of the Office Action -- Rejection of Claims 1-3, 6-9, 21-25, 36, 38, 39, 42-44, 67, 47-71, 74-76, 82 and 86-88 under 35 U.S.C. 103(a) over Funakoshi et al in view of Bjorck et al and de Boer (US Patent No. 5,874,082) as evidenced by Uckun et al.

The Examiner rejected claims 1-3, 6-9, 21-25, 36, 38, 39, 42-44, 67, 47-71, 74-76, 82 and 86-88 under 35 U.S.C. 103(a) over Funakoshi et al in view of Bjorck et al and de Boer (US Patent No. 5,874,082) as evidenced by Uckun et al. Applicants respectfully traverse this rejection.

Applicants do not concede to the Patent Office position; Applicants are amending the claims solely to obtain expeditious allowance of the instant application. Applicants have canceled claims 1-3, 6-8, 38, 39, 42-44, 67, 47-51, 55, 58, 59, 62-65, 68, 70-71, 74-76, 82 and 86-88, without prejudice to refile, thereby rending the rejection to these claims moot.

Neither Funakoshi (see pg 2793 of Funakoshi, submitted in the IDS dated Nov. 28, 2000 as document AZ, title of Reference No. 11, which discloses that "CD40 MABS M2 and M3 *inhibit* CD40L binding and function") nor Uckun (which discloses CD40 antibody G28-5, page 2450, col 1, line 27; see also pg 3, lines 34-36 and page 54, lines 24-29 of the present application where it is disclosed that G28-5 *does not potentiate* CD40/CD40L interaction) nor Bjorck (see page 434, right hand column and Table 4)

teach increased binding of CD40 to CD40L as claimed. Actually, all three teach away from antibodies which increase the binding of CD40L to CD40 as claimed in independent claims 9, 21-24, 36, and 69.

Bjorck specifically discloses *the inhibition of binding* of CD40 to CD40 ligand on page 434, second column, lines 14-19 as follows "[w]hen investigating the ability of the antibodies to interfere with binding of CD40-ligand all three mAb" (i.e. 17:40, mAb89, and S2C6) "*were to different extents able to do so....*" (emphasis added). Bjorck discloses that S2C6 blocked binding of CD40 to CD40L up to 50%.

de Boer does not satisfy the deficiencies of any of the three above references in failing to teach the increased binding of CD40 to CD40 ligand. de Boer does not teach or suggest an antibody which would increase the binding of CD40 to CD40 ligand. Therefore, this combination of references cannot render the claims 9, 21-24, 36, and 69, nor any dependant claims therefrom, obvious. Claims 9, 21-24, 52-54, 56, 57, 60, 61, 66, and 69 are non-obvious over Funakoshi et al in view of Bjorck et al and de Boer (US Patent No. 5,874,082) as evidenced by Uckun et al. Applicants respectfully request withdraw of this rejection.

10. **Paragraph 14 of the Office Action - Rejection of Claims 1-9, 21-24, 38, 39, 42-44, 47-60, 62-66, and 68-91 under 35 U.S.C. 103(a) over Francisco et al (The Journal of Biological Chemistry, 1997, Vol. 272, pp. 24165-24169) in view of Paulie et al (Cancer Immunology, Immunotherapy, 1985, Vol. 20, pp. 23-28) and de Boer (US Patent No. 5,874,082) and Schlom (Molecular Foundations of Oncology, S. Broader, Ed. 1991, pp. 95-145).**

The Examiner rejected claims 1-9, 21-24, 38, 39, 42-44, 47-60, 62-66, and 68-91 under 35 U.S.C. 103(a) over Francisco et al in view of Paulie et al and de Boer (US Patent No. 5,874,082) and Schlom. The Applicants respectfully traverse this rejection.

Applicants do not concede to the Patent Office position; Applicants are amending the claims solely to obtain expeditious allowance of the instant application. Applicants have canceled claims 1-8, 38, 39, 42-44, 47-51, 55, 58, 59, 62-65, 68, 70-71, 74-76, and 79-91, without prejudice to refile, thereby rending the rejection to these claims moot.

The Examiner alleges that Francisco teaches "bryodin fused to the sFv fragment of the G28.5 antibody which binds CD40 is cytotoxic to a non-Hodgkin's lymphoma cell line, a multiple myeloma cell line, a B-cell leukemia and a Hodgkin's disease cell line. Francisco et al teaches that all these cell lines express CD40." Further, the Examiner alleges that Francisco et al teaches that "because bryodin kills cancer cells, it is concluded that bryodin is a chemotherapeutic agent. Francisco et al also teach that G28.5 fused to Pseudemonas exotoxin was toxic to lung, breast, colon and ovarian carcinoma cell in vitro."

The Examiner alleges that Paulie et al teach that "S2C6 antigen is found on bladder cancer cells and on B lymphocytes." The Examiner further alleges that Paulie teaches that "the S2C6 epitope is part of the CD40 receptor (abstract, lines 1-3)." The Applicants respectfully assert that the abstract of Paulie does not teach that "the S2C6 epitope is part of the CD40 receptor" as suggested by the Examiner.

The Examiner alleges that de Boer teaches "how to make humanized anti-CD40 antibodies." The Examiner admits that de Boer does not teach how to make a humanized anti-CD40 S2C6 antibody.

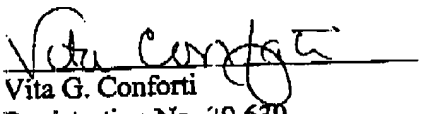
The Examiner alleges that Schlom teaches the answer to the HAMA response is "humanization of murine antibodies." The Examiner further alleges that Schlom teaches that "single chained antibodies and Fab antibody fragments have increased ability to penetrate through tumor masses in contrast to whole antibodies."

The Examiner has not shown where, either alone nor in combination, Francisco et al, Paulie et al, de Boer and Schlom et al teach or suggest "increases the binging of CD40 ligand to cell surface CD40 on B cells by at least 45%" as claimed in independent claims 9, 21-24, and 69. Accordingly, the present claims would not be rendered obvious by the cited articles. Claims 52-54, 56, 57, 60, 66, 72-73, 77, and 78 are dependent claims and distinguish for at least the same reasons as their independent base claims. Therefore, the Applicants respectfully requests that the instant obviousness rejection be withdrawn.

CONCLUSION

Applicants assert that in view of the above amendments and remarks, the Examiner's rejections have been successfully overcome and the application is in condition for allowance. Applicants respectfully request further action commensurate therewith. Applicants invite the Examiner to telephone the below indicated attorney at (425) 527-4122 if any questions remain.

Respectfully submitted,



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